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*Review scientific paper***DISEASES THAT CHANGED THE WORLD****Željko CVETNIĆ^{1*}, Darko MAJNARIĆ¹, Branko BAČANEK¹, Jadranka JURMANOVIĆ¹,
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Abstract: Different contagious diseases had huge impact on the society during the history. Their appearance destroyed and devastated whole territories, caused number of victims which drastically surpassed the ones in wars, and after the appearance of such disease the whole path of the history changed. The most important contagious diseases are known and written in the earliest known records, from the beginning of the world they were humans' companion, their impact on the development, suffer and death is huge during hundreds of years. Smallpox belong to the most deadly and the scariest viral diseases faced by humanity.

Pandemic of Spanish flu from 1918 is the biggest global demographic earthquake that the world has ever experienced. One of the most important transmissive (vector) mosquito-borne diseases, caused by protozoa, is malaria. Lice transmit the causer of typhus fever, trench fever and recurrent fever. Plague in natural habitats transmits rat flea and it is one of the most dangerous bacterial diseases. Typhus fever was a constant companion of the distress, accidents and suffering of the people during wars. Many faiths of people were connected with tuberculosis, it was always an unavoidable part of living community. Leprosy is one of the oldest and scariest diseases. It was a synonym for stigmatization and discrimination because of big deformations on the body. Syphilis is constant and unwanted companion of humanity for more than 400 years. Since its first occurrence, syphilis was stigmatized, disgraceful disease. Contemporary past of cholera began in 1817. Cholera causes difficult clinical diseases followed by humans pain and panic, and disrupts social and economic structure and development of the society wherever it occurs. It is visible that throughout the whole history, contagious diseases had huge impact on development and prosperity of the humanity. Throughout the history, humans had many important wars and battles, but perhaps the biggest ones were fought, and many of them are still fighting, against the contagious diseases.

Key words: diseases, history, world

INTRODUCTION

Contagious diseases were always attracting the most attention because of their mass occurrence, high mortality rates among patients and far-reaching consequences that they were causing. Human recognized the disease as a weakness and powerlessness of the body. They were described with simple descriptions and general symptoms so it was very difficult recognizing

the type of disease. They were endangering the health, and the dangerous ones even the life, especially if they were occurring as epidemics. During the past, huge epidemics were effecting the faith of particular nation, they were weakening the strength of powerful and big armies, causing the hunger and misery. Different doctors, histo-

rians and different chroniclers write about the epidemics of contagious diseases, so from their conclusion we can find out about the suffering of the humanity throughout the history. Old cultural peoples have met many horrors of contagious diseases. Diseases, their occurrence and spread are consistent with understanding of medicine of that particular time. Usually, epidemics are considered a supernatural cause, and later a God's punishment (Glesinger, 1978).

Contagious diseases are still highly ranked on cause-of-death scales (in some parts of the world they are number one). Around 15 million people every year die because of the contagious disease. Some of the traditional contagious diseases are suppressed in developed countries, but the new ones with new causers occurred, new

clinical pathology picture and with new problems for public health (Jeren, 2006).

In this review, contagious diseases that are dangerous and written in the earliest known records will be described shortly. About the diseases that were the enemies of the humanity throughout the history, their influence on the development, suffer and death that were caused in humans during thousands of years. Described are the most important diseases that occurred until the end of 19th century, and at the beginning of 20th (spanish flu), and some of them are active even today. The selection was driven based on the meaning and the importance of the disease as well as their influence on the happenings throughout the history (Cvetnić, 2018).

HISTORY

According to the discussions that were attributed to Hippocrates (460-377. B.C.), disease is the loss of natural harmony, deviation from the rule, breaking of the ideal relationship between the parts of harmonious continents. That is, according to Hippocrates, overall and local disorder withing four basic fluids of the human body (blood, mucus, yellow bile and black bile). Health is harmonious arrangement of basic fluids, and the diseases is a lack of fluids or their imbalance. The number of diseases is unlimited because there are infinite number of possibilities and imbalances between the fluids and the body (Grmek, 2000). Hippocrates dismissed supernatural causes of epidemical diseases, because all of them have natural causes. He believes that in air, water and rot harmful things are present, contagious evaporations that he calls miasmas. They spoil the air and human inhales them throughout the air, and in the organism they cause spoilage of body fluids. Mass occurrence of the disease is caused because at the same time many people inhale such toxic stuff, which cause the same diseases in all of them. That is how Hippocrates describes the beginning of epidemical diseases. However, neither Hippocrates nor other doctors

don't know any protective measures that would help preventing the occurrence of such epidemic. The only thing that humans were doing during epidemics is running from the diseases (Glesinger, 1978).

The history of the world is interweaved by the influence of many different contagious diseases on human population. The evidences of pox were found on Egyptian mummy. Ebers papyrus in Egypt are painted with the pictures of contagious diseases, and contain recipes and instructions how to treat many diseases. Hippocrates was writing about the spread of the disease through air and water, he connected the climate, nutrition and environmental conditions as important factors in the occurrence of contagious diseases. Fracastoro was, at the beginning of the 16th century, pointing out that the diseases were caused by small, invisible bodies (germs), he recognized that diseases can spread by direct touch or with the object, and that it is possible to spread the infection from the distance (through air). None of them are spread by an occult force, which was thought by the old medicine, and the new, evolved principles are being accepted. The evolution of microscope in 17th century enabled

the visualization of microorganisms. At the end of 19th century, important causers of the most important bacterial diseases were found, as well as their breeding and identification. Different vaccines were developed and used in order to control disease, as well as the the different measures for controlling and preventing the most im-

portant diseases. 20th century brought chemotherapy and antibiotics. Than it could be said that almost all practical problems in suppression and control of contagious diseases that have appeared until than, were solved (Bracham, 2003)

SMALLPOX

Smallpox belongs to deadliest and the most scariest viral disease faced by humanity during history. Only during XX century smallpox epidemic caused death of 300 to 500 million of people. It is considered that they are responsible for death of 10% of the people in the world, during last thousand years (Thevez et al., 2014). In China, as early as the tenth century, the first protection against smallpox was made by blowing powdered dried scabs into the nose, removed from smallpox patients. Later, variolation procedures were applied until vaccination with cowpox virus was first applied by Edward Jenner in 1796, followed by vaccination worldwide (Behbehani, 1983). This process has protected humanity and contributed to significant demographic growth later (Thevez et al., 2014). By the mid-twentieth century, smallpox was widespread in the world and endemic in many countries, and at the time it was still suffering from 10 to 15 million people worldwide, dying about two million. In 1967, the World Health Organization adopted the Smallpox Control Program.

For the next ten years, with the use of vaccination, the last smallpox case was reported in Somalia in 1977, and in 1980 the WHO declared the world free from smallpox. Smallpox is the first and so far the only disease in the world that human have suppressed by vaccination and other public health measures. Smallpox has killed more people in the world than all wars in history (Morse, 2009). The genus that includes variola virus, the causative agent of smallpox, includes the vaccine virus, monkeypox and cowpox virus, the camelpox virus, and all of these species are zoonoses. Recent studies indicate that in the future it is possible to expect the evolution of zoonotic orthopoxviruses and the emergence of a new variol-like virus (Shchelkunov, 2013). There are still virus samples in laboratories in the US and Russia. When using the smallpox virus as a biological weapon, the consequences could be very devastating, because for almost 40 years no one has been vaccinated against smallpox.

SPANISH FLU

As we think today about the threat of an influenza virus that will evolve and as recombinant and highly pathogenic will come back again, we can not bypass the story of the 1918 flu pandemic. The 1918 flu pandemic is one of the paradigms of a nightmare that comes up when deadly infectious diseases are mentioned. Spanish flu was, by all accounts, the greatest natural disaster of the early 20th century. Official estimates of the mortality caused by the flu are steadily rising as researchers continue to find data in developing countries and distant places (Morse, 2009).

At the beginning of the 20th century, studies showed that 21.5 million people died from the consequences of the Spanish flu. And more recent studies estimate that they range from 50 to even up 100 million people. It is estimated that one third of the world's population at that time, or about 500 million people, were infected and had clinically visible signs of the disease. That's why they call the Spanish flu "the mother of all pandemics" (Taubenberger and Morens, 2006). No monster, no war, no starving in human history has ever killed so many people in such a

short period. The 1918 Spanish flu pandemic is the largest global demographic earthquake the world has ever experienced. The Spanish flu was in the shadow of World War I, although it took significantly fewer human lives (approximately 8 to 10 million). The Great War lasted longer, with great media attention. The public accepted the flu as an extension of war casualties, and one of the reasons was that each wave of the Spanish flu lasted briefly and it would disappear again for several months (Anušić, 2015). The 1918 Spanish flu pandemic was so deadly, and if the Spanish flu appeared today and killed the same

percentage of the American population, more than 1.5 million Americans would die. It would kill more people in one year than die each year of heart disease, cancer, stroke, chronic lung disease, AIDS and Alzheimer's. The epidemic affected the course of history, killing more Americans in one year than that were killed in the battles of World War I, World War II, the Korean War, and the Vietnam War (Kolata, 2001). The Spanish flu can be considered a "historical" accident and a cruel consequence of the Great War (Erkoreka, 2009).

MALARIA

Vectors (mosquitoes, ticks, fleas, lice, and others) are carriers of various agents of transmissible (vector) infectious diseases from one infected person to another or from an infected animal to a human. Malaria is one of the most important mosquito-borne transmissible (vector) diseases, caused by protozoa. Malaria has been called the queen of the diseases, it has been known since time immemorial. It occupies a unique place in historical annals. Some believe that it is responsible for the collapse of the Roman Empire. Throughout history, its victims have been princes, kings, and great conquerors, and during the 20th century alone, it caused the deaths of between 150 and 300 million people. Ancient scriptures and various artifacts testify the long rule of malaria (Carter and Mendis, 2002). In his book of malaria, Chloupek (1939) describes malaria as the largest empire in the world, and such a malarial empire is, for man, an empire of sadness and distress. He mentions the areas of Macedonia, where he served after World War I, as malaria endemic. In these villages, people are as gray as their houses, yellow-gray as burned land. If you look into their eyes, the mirror of the soul, than that soul is one of the great sufferings. The construction of the Panama Canal was an unique example of how disease can hinder human progress. The Panama Canal was one of the largest,

most ambitious and significant engineering projects in modern history. It was also one of the deadliest ventures in the world. Work was stopped after several years because of the high mortality of workers on the project. More than 27 000 people are thought to have died from the disease and the consequences, with malaria being the main cause (Walker, 2014). Prevalence of malaria depends on the prevalence of the vector, a mosquito of the genus *Anopheles*. As many as 70 species of mosquitoes of this genus have the ability to transmit the cause of malaria (Sinka et al. 2012). Quinine played an important role during colonial conquests, where whites faced tropical diseases and also influenced war outcomes throughout the history (Curtin, 1990, Bruce-Chwatt, 1988, Brabin, 2014). More than a century after the identification of the parasite that caused malaria and more than half of century after the mosquito repellents and drugs were found to be effective, hundred of millions of people still suffer from malaria and hundreds of thousands die, especially in the poorest parts of the world. Malaria is the fifth cause of death in the world. In many parts of the world malaria is still the "disease queen" and its "empire" is still in existence.

PLAGUE

Plague is one of the most dangerous bacterial diseases. It is considered that it accompanies people for a long period of time, described since ancient time. In Scripture, all the troubles man experienced, including hunger and plague, were a punishment for sinners. Plague was synonymus for sickness, misery and suffering, dying from the plague in terrible torment was one of the anathema (Dodig, 2013). The plague epidemic marked the entire period of the late and part of the early Middle Ages. The effect of the plague becomes significant for the history of the mankind. The chronicler states that "*the plague has spared no place where man lives, no island or cave, no mountain peak...*" (Meyer,

1961). The causative agent is maintained among the wild rodent population, the vector is rat flea, which spreads the causative agent among rodents. Plague has disappeared from Europe for a long time, but is still smoldering in hotspots around the world, like Asia, Africa, North and South America. It cannot be eradicated because it is widespread in natural reservoirs. In many cases, it is shown to be a re-emergent disease, which recurs after many years and continues to pose a threat to public health in many countries.

TYPHUS FEVER

Typhus fever (epidemic) is caused by *Rickettsia prowazekii* transmitted by body lice which is infected by suckling the blood of patients at the rickettsial stage. It played a key role during the wars in Europe between the 15th and 20th centuries. The largest known epidemic of typhus fever affected Napoleon's army during the military invasion of Russia. More than 500,000 soldier are thought to have died from cold weather and infectious diseases, and one of the most significant was typhus fever (Raoult et al., 2004). Typhus fever has been reported in Bosnia and Herzegovina, and it began to spread especially rapidly after 1945 immediately after World War II. In 1945, one hundred outbreaks of typhus fever occurred, with the highest incidence in Europe of 215/1000 in epidemic areas. In the control of disease, the guidelines of a unique program have been used worldwide to eradicate disease. Since 1971, there have been no more reported cases of typhus in Bosnia and Herzegovina and the disease has been eradicated (Puvačić et al., 2006). The 1883 book of August Hirsh reads: "The history of typhus is written as the dark page of a world story, that affected humanity during wars, misery, suffering and pain of every kind..." (Snyder, 1947).

Between the 1950s and the 1980s, large outbreak of typhus fever became less frequent and geographical distribution declined due to improved living standards. During this period, sporadic cases of zoonotic origin (in the US) and Brill-Zinser's disease have been reported in the literature. Infection with *R. prowazekii* have been rarely reported in the US, and from 1976 to 2001, a total of 39 cases of typhus fever were reported in persons who had no lice and were not in contact with lice. Almost all of these cases were in the eastern United States. In most cases, direct or indirect contact with flying squirrels (*Glaucomys* spp) or with nests of flying squirrels before the onset of the disease has been demonstrated (Reynolds et al., 2003). Major outbreaks of typhus fever have mainly occurred in Africa, with cases reported in Burundi, Ethiopia and Rwanda. In Ethiopia, the annual number of cases of typhus ranged from 7.000 to 17.000 (except in 1979, when more patients were diagnosed). In the 1970s, the largest epidemic occurred in Burundi and Rwanda. In 1975, 9.000 cases of typhus fever were reported in Burundi (WHO, 1997). During the 1980s and 1990s, typhus fever was found in poor parts of the world, always associated with poor sanitation (such as prisons

of refugee camps) and the colder climate in mountains areas. One of the more important and major epidemic was recorded in Ethiopia in 1984 when close to 4.000 patients were registered (*Ndihokubwayo and Raoult, 1999, Letaief, 2006, Labruna, 2009*). In recent decades, there have been occasional outbreak in Africa (Ethiopia, Nigeria, Burundi, Rwanda, Uganda), Mexico, Central America, South Amerika (especially Peru), Eastern Europe, Afghanistan, India and China. In North Africa, Russia and Kazakhstan sporadic cases or small suspected outbreak have been identified.

TUBERCULOSIS AND LEPROSY

Two important and unavoidable diseases caused by mycobacteria are tuberculosis and leprosy. Tuberculosis and leprosy exist since pre-historic times. Many human destinies have been associated with tuberculosis, it has always been integral part of community life. Nowhere in the ancient record is there a record of its beginning, but throughout the history it has always been present. Where other outbreak lasted weeks or months, the tuberculosis epidemic would last for a century or longer. Tuberculosis slowly and quietly entered in homes by creeping into the homes of millions of people, once arrived and never left again. It affected large number of people, and very often it was children and young people at the beginning of their lives that had a wide social impact. In 19th century it seemed as everyone was dying from tuberculosis. Tuberculosis has become a popular phenomena, first as romantic redemption, and than as a reflection of social ills (Morens, 2002). Numerous life destinies were associated with tuberculosis, book work were dedicated to it through character des-

In addition to typhus fever, lice transmit recurrent and trench fever. Diseases have been known for centuries and their occurrence is most present during wars. They continue to be a major public health concern in a population of people living in poor hygiene conditions due to war, various social disorders, hunger and poverty. In developed countries, diseases are often proven in homeless, and in developing countries epidemic of these diseases have been reported in prisons and refugee camps (*Badiaga and Brougui, 2012*).

cription or through the illness of the artist himself. Many poets and painters died of tuberculosis leaving behind a large oeuvre (Dugac, 2005, Vrga, 2012). According to the World Health Organization around two million people in the world still die from tuberculosis today, and about eight million are affected (Jeren, 2006).

Leprosy is one of the oldest and most terrible diseases that people get sick with. It has been synonymous with stigmatization and discrimination due to major deformities on the body. It has long been known as "*death before death*". Despite therapy, it is still endemic in some countries (Visschedijk et al., 2000, Dogra et al., 2013). Annually, 200,000 new leprosy patients are diagnosed. According to the WHO data in 2015, leprosy was reported in 136 countries of the world, and there are approximately four million people with disabilities caused by leprosy in the world. Leprosy has long been thought to be just a disease of man, but natural reservoirs of leprosy have been proven to be nine-banded armadillo in the US and South America (Truman et al., 2011).

SYPHILIS

Syphilis has been a constant and unwanted companion of humanity for over 400 years. Syphilis have been a stigmatized, shameful disease from the first onset. It has affected the lives

of millions of people among all social layers. It is known that many celebrities, various artists, writers, composers and great historical figures have been infected with syphilis. Syphilis did

not choose the level of social and economic status, it affected everyone. Syphilis is a hundred-face disease and a great imitator. This old enemy of humanity, thought to be on the verge of defeat after the discovery of penicillin, once again sur-

prised and returned continuing to attract humanity's attention. In the last 30 years, due to homosexual habits, drug abuse and HIV infection, the number of infected persons has increased again, which is a public health problem (Marinović and Lipozenčić, 2002).

CHOLERA

The modern history of cholera began in 1817 when explosive cholera outbreaks began to occur in the Bengal region along the Ganges River in the Indian subcontinent, where the disease is endemic. It was the first of seven cholera pandemics to date that have hit almost the entire world and caused millions of deaths (Siddique and Cash, 2014). Outbreaks of various diseases were very common during the 19th century, and especially difficult during cholera, which caused very high mortality. The number of deaths caused great panic, and particular fear and disbelief

were triggered by the symptoms that turned the human body into a wreck, which made this disease a terrible monster that people were terrified off (Ipšić, 2010). Cholera outbreaks cause human suffering, panic, disruptive social and economic structure as well as community development wherever they occurred. Natural disasters such as tsunamis, earthquakes and war significantly increase the risk of epidemics with high mortality rates.

EMERGENT AND RE-EMERGENT DISEASES A NEW THREAT TO THE WORLD?

It is evident that, throughout the history, infectious diseases have had a significant impact on the development and prosperity of humanity. Some diseases are suppressed or under control in developed countries, but in the undeveloped ones, they survive and affect millions of people. By the end of the twentieth century, almost everyone was convinced that treatment, vaccination and other interventions would soon be able to eradicate most infectious diseases. However, smallpox have been eradicated, but the results are disappointing in the fight against malaria or tuberculosis, which are still a problem. So it's not often about eradication, it's just about controlling endemic diseases.

After the appearance of emergent and re-emergent diseases was noted, the Institute for Medicine of the US National Research Council in 1991 appointed a nineteen-member multidisciplinary committee to study the occurrence of the new pathogens that threaten the health of the

nation. Emergency infectious diseases are those that appear for the first time in a population, and re-emergent ones are those that reappear in a certain period of time in a place where they have been previously eradicated. Their report from 1992 was entitled: "*New infections – a microbial threat to US health*". Thought the discussion, it was concluded that there are six different factors that can explain the occurrence of emergent and re-emergent infectious diseases. These factors are: human demographics and behavior, technology and industry, economic development and land usage, international travel and the market, microbial adaptation and change, and the collapse of public health measures (Brachman, 2003). Emergency infectious diseases represent a significant burden on global economy and public health. Between 1940 and 2004, 334 emergent infectious diseases appeared worldwide. The highest incidence was in 1980s, at the same time as the onset of the HIV pandemic. Zoonoses (60.3%) are dominant, and most zoonoses

(71.8%) originate from wild animals. It was stated that in 54.3% of the cases the bacteria and rickettsiae were the causative agent, in 25.4% the viruses were the cause, in 10.7% of the protozoa, in 6.3% of the fungus and in 33.3% of the helminths (Jones et al., 2008).

Exactly 100 years ago, the Spanish flu virus was present all over the world. Various very similar and altered avian influenza (H5N1) virus, the pandemic (new) influenza A (H1N1) virus, or some other types such as H7N9, still brings fear, disturbance and death to certain parts of the world today. In 1977, the World Health Organization announced that smallpox has been defeated, a viral disease that has caused the highest number of deaths in history. However, just a few years later, in the 1980s, a new virus, the Acquired Immunodeficiency Syndrome (AIDS) emerged, which again terrified the world with its appearance and consequences. It is a syndrome of acquired immunity deficiency, which leads to a state of impaired immunity, which results in the appearance of various diseases that would not occur in healthy people. According to the World Health Organisation, 36.7 million people were living with AIDS in 2016, 1.8 million were newly diagnosed, and one million died from the disease (HZJZ, 2017). In the United States, a flu-like disease appeared in the Four Corners region in 1993. The patients developed severe pneumonia and died. The virus was initially named *Sin Nombre* (SNV) (Spanish-no name), later identified as hantavirus, and the virus's natural reservoir is the mouse (*Peromyscus maniculatus*). The disease is rare but very serious and often fatal (up to 66.7%) (Torres-Perez et al., 2010). Hendra virus infection is a rare zoonosis that causes severe and often fatal disease in infected horses and humans. A mare with flu-like symptoms get sick, and a two people get sick with the same disease, and a horse owner died of lung and kidney failure. Later in Australia, dozens of cases were described in horses and humans. Virus reservoirs are bats. The virus was first described in 1994 in Hendra, a suburb of

Brisbane, Australia (Field, 2016). In 1997 encephalitis and respiratory diseases in pigs were identified in Malaysia. Shortly after, farm workers began to become sick with encephalitis. Over the two-year period, there were several hundred cases of disease in people with more than 100 deaths. A nipah virus was isolated from the brain of a patient who died. It was paramyxovirus with similar characteristics to the hendra virus, and the reservoirs were found in bats from the genus *Pteropus* that are fed by fruit (Carter and Saunders, 2007, Ang et al., 2018). The West Nile virus was known as early as 1937 when it was isolated from a woman's blood in the West Nile area of Uganda. In 1996, infections were reported in Europe and in 1999 in the US. West Nile virus infection is a typical vector-borne zoonosis. It is mostly asymptomatic (in 80% of cases), in 20% of infected it is manifested as a non-specific febrile disease, and in less than 1% of patient there is a neuroinvasive disease manifested by meningitis and encephalitis. Different species of birds are the primary hosts and reservoirs of the virus, and the main vectors are mosquitoes (Carter and Saunders, 2007). 15 years ago (2003) SARS (*Severe Acute Respiratory Syndrome*) appeared in China. It is a severe viral respiratory disease that can cause mortality in up to 15% of diseased people (Krajinović and Baršić, 2003). In 2012, a new global threat, a disease called MERS (*Middle East Respiratory Syndrome*) which causes a serious respiratory illness, appeared in Saudi Arabia. Although most patients are geographically related to the Arabian Peninsula, MERS has also been detected in other parts of the world. The hosts of the virus are camels and interhuman transmission has been demonstrated. In the Middle East, mortality was as high as 25.9% and 20.4% in South Korea (Park et al., 2018). According to the World Health Organization, from 2012 to date, the disease have been proven in 27 countries. During 2013, the world was altered by the emergence of a terrible viral Ebola disease that has occurred in West Africa. Millions of people were affected and thousands more became ill. The disease is

zoonosis, and the virus have been proven in gorillas, chimpanzees, fruit bats and antelopes (Jermeršić, 2014).

CONCLUSION

Historically, infectious diseases have had a profound impact on the human population, including its evolution and development. The onset of the disease is not a simple occurrence, it is dynamic, most new diseases are not caused by new agents, they are mostly known, but they reappear in different circumstances, in a different way, many disease have changed their image and impact. An increasing number of potentially pathogenic (opportunistic) microorganisms are emerging. It is known that 10-15% of infectious agents can also cause malignancies. They can be identified and recognized because of the new and highly sensitive techniques of proof. Human activities contribute to the emergence of disease, and various social, economic, political, climatic,

technological and environmental factors can influence and shape its occurrence. The realization that infectious diseases can be completely defeated has been doubted in recent years by the appearance of emergent and re-emergent diseases. Despite the advances in medicine, scientists have not yet found a permanent solution in some areas of the world for long-known diseases such as malaria, tuberculosis or cholera. The spectrum of infectious diseases is expanding, and the problems of infections are present in all aspects of medicine, it is increasingly complex, and the challenges are increasingly demanding. It is clear that, at the beginning of the new millennium, infectious diseases are a major and ongoing threat to today's society and continue to be one of the greatest killers in the world.

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